VITAMIN D TESTING
Policy Number: CMP-038
Effective Date: January 21, 2017

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This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this Medical Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply.
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BACKGROUND

Vitamin D has two forms, ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3), and several metabolites. The main source of vitamin D comes from the skin through exposure to solar ultraviolet B light. Also, vitamin D3 can be obtained from the diet such as deep sea fatty fish, egg yolks, liver, or from supplements. Vitamin D2 is found in some plants in the diet and is produced commercially by irradiation of yeast. Both vitamin D2 and D3 are available through supplements.

Few foods naturally have substantial vitamin D content, and dietary vitamin D is obtained primarily through fortified foods or supplements. Both forms of vitamin D are converted to 25-hydroxyvitamin (25(OH)D) in the liver, and later hydroxylated in the kidney and other tissues to 1,25-dihydroxyvitamin D (1,25(OH)2D), which is the only biologically active form of vitamin D.
Classical actions of vitamin D include the regulation of calcium and phosphorus homeostasis and the development and maintenance of the skeleton. The synthesis of 1,25(OH)\(_2\)D is tightly regulated and stimulated primarily by serum parathyroid hormone (PTH), as well as low serum calcium or phosphorus levels, and inhibited by circulating FGF23 produced by osteocytes. 1,25(OH)\(_2\)D acts in the intestinal cell to increase calcium absorption or in the bone to stimulate differentiation and activation of osteoblasts and osteoclasts.\(^1-^3\)

There is a significant clinical evidence of the adverse health outcomes for the patients with low vitamin D levels even when the most conservative cut-offs are used for the determination of the vitamin D status. Recently, research also suggests that vitamin D may provide protection from osteoporosis, hypertension (high blood pressure), cancer, and several autoimmune diseases. Supplementation without baseline 25(OH)D measurement is recommended for dark-skinned or veiled subjects not exposed much to the sun, individuals > 65 years without musculoskeletal health problems, cardiovascular disease, autoimmune disease or cancer, and institutionalized subjects.\(^4\)

**Associations with Adverse Health Outcomes**

Vitamin D has been described as an immunomodulator targeting various immune cells, including monocytes, macrophages, T-lymphocytes, and B-lymphocytes.\(^5\) Studies have suggested that vitamin D plays an important role in maintenance of the immune system. Vitamin D may have a central role in infectious and autoimmune diseases, in particular tuberculosis and type 1 diabetes.

Vitamin D influences the immune response to tuberculosis, and vitamin D deficiency has been associated with increased tuberculosis risk in different populations.\(^6\) A meta-analysis explored the association between low serum vitamin D and risk of active tuberculosis in humans.\(^7\) After review of studies published between 1980 and 2006, low serum vitamin D levels are associated with higher risk of active tuberculosis.

Similarly, Ginde et al. (2009) performed a secondary analysis of 18,883 participants in NHANES III population age 12 years and older and examined association between 25(OH)D levels and recent upper respiratory tract infection.\(^8\) Lower 25(OH)D levels were independently associated with recent infection. Odds ratio for patients with 25(OH)D levels of <10 ng/mL was 1.36 compared with patients with levels of 30 ng/mL and above.

Low levels of vitamin D have been associated with a higher risk of cardiovascular disease and myocardial infarction.\(^9,^{10}\) A study of over 18,000 men, free from cardiovascular disease ages 40 to 75 years, was conducted with 10 years follow-up.\(^11\) Men with 25(OH)D levels less than 16 ng/mL were at 2.42 times higher risk of developing infarction than those with levels >29 ng/mL. Similarly, Wang et al. (2008) reported on 1739 participants without prior cardiovascular disease and those with 25(OH)D levels less than 10 ng/mL had cardiovascular hazard ratio of 1.80 comparing with the ones with higher concentrations.\(^12\) Likewise, there have been reports of clinical and epidemiological studies that suggest there may be an association between hypertension and vitamin D status as well as calcium metabolism.\(^13\)

There have also been reports of an association of low levels of vitamin D and an increased cancer risk.\(^14\) In one study, Wu et al. (2007) reported that levels of vitamin D are inversely associated with colorectal cancer risk.\(^15\) In a nested case-controlled study of 179 colorectal cancer patients and 356 controls, higher 25(OH)D plasma concentrations were statistically significantly associated with decreased risk for colorectal cancer (highest quintile versus lowest quintile). Another study examined 304 patients who were diagnosed with colorectal
cancer from 1991 to 2002 and had follow up until 2005. The higher 25(OH)D levels were associated with a significant improvement in overall survival.

A Summary of Existing Guidelines and Recommendations

In November 2010, the Institute of Medicine (IOM) report “Dietary Reference Intakes for Calcium and Vitamin D” revised the previous recommendations and set the average requirement for North Americans of 400 IUs of vitamin D per day and for people age 71 and older as much as 800 IUs per day. It also identified the specific subgroups (older, institutionalized people, and dark skinned people) who are at increased risk of getting too little vitamin D.

In 2003, the National Kidney Foundation issued a “K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease”. It defined the vitamin D status as:

- Severe deficiency - 25(OH)D: <5 ng/ml
- Mild deficiency – 25(OH)D: 5 – 15 ng/mL
- Insufficiency – 25(OH)D: 16 – 30 ng/mL

This report also set up a recommendation on the frequency of the laboratory testing for vitamin D in patients with CKD stages 3 and 4: after 6 months from start of supplementation, once the patient is sufficient – annual reassessment.

In 2008, the American Academy of Pediatrics (AAP) issued guidelines “Prevention of Rickets and Vitamin D Deficiency in Infants, Children, and Adolescents” that defined vitamin D deficiency in adults as 25(OH)D concentration of <20 ng/mL and insufficiency as concentration of 20 – 32 ng/mL. The guideline recommended that 25(OH)D serum concentration in infants and children should be greater or even 20 ng/mL. It also stated that “a mother should be supplemented with adequate amounts of vitamin D₃ to ensure that her 25-OH-D levels are in a sufficient range (>32 ng/mL).”

In 2009, a Vitamin D international Summit Meeting issued clinical practice recommendations “Vitamin D and Musculoskeletal Health, Cardiovascular disease, Autoimmunity and Cancer: Recommendations for Clinical Practice”. The expert panel clearly outlined recommendations as listed below:

Individuals with or at risk for musculoskeletal health problems, cardiovascular disease, autoimmune disease, and cancer in whom it is recommended to measure serum 25(OH)D level in clinical practice include:

- Individuals with or at risk for osteoporosis
- Elderly subjects with a recent fall accident
- Pregnant women
- Patients with chronic kidney disease stage 4 – 5D
- Transplant patients
- Patients with conditions or treatments that can lead to bone loss
- Obese individuals
- Patients with diabetes
- Hospitalized patients
- Patients with bone/muscle pain or aches
- All individuals with hypertension
- Patients with autoimmune disease
- Subjects at high risk for autoimmune disease
- Patients starting or already on corticosteroids
- All cancer patients undergoing treatment

- Optimal levels for outcomes in musculoskeletal, cardiovascular health, and cancer for 25(OH)D is 30 – 44 ng/mL
- 25(OH)D level for individuals at risk for musculoskeletal health problems, cardiovascular disease, autoimmune disease, and cancer should be above 30 ng/mL
- Proposed an upper safety limit for 25(OH)D of 100 ng/mL
- As a rule of thumb, an intake of 1000 IU vitamin D per day results in increase of approximately 10 ng/mL in 25(OH)D, although individual responses are variable
- Supplementation without baseline 25(OH)D measurement is recommended for dark-skinned or veiled subjects not exposed much to the sun, individuals without musculoskeletal health problems, cardiovascular disease, autoimmune disease, and cancer 65 years old and above, and institutionalized subjects. For those individuals a dose of 800 IU per day with intermittent dosing regimen is recommended
- Measurement (monitoring) of serum 25(OH)D is recommended after at least 3 months of supplementation. Further monitoring is recommended according to physician judgment

In 2010, the Mayo Foundation published a review for clinicians “Vitamin D Deficiency in Adults: When to Test and How to Treat”. The review point on the clinical risk factors for vitamin D severe deficiency such as:
- Inadequate oral intake of vitamin D
- Malnutrition
- Limited sun exposure
- Malabsorption including
  - Short bowel syndrome
  - Pancreatitis
  - Inflammatory Bowel Disease
  - Amyloidosis
  - Celiac Sprue
  - Malabsorptive bariatric surgery procedures
- Some antiepileptic medications
- Severe liver disease or failure
- Aging
- Renal insufficiency, glomerular filtration rate <60
- Nephrotic syndrome

In 2005, the American Society for Nutritional Sciences published a report from a symposium “Vitamin D Insufficiency: A Significant Risk Factor in Chronic Diseases and Potential Disease-Specific Biomarkers of Vitamin D Sufficiency”. Part of it was titled “Circulating 25-Hydroxyvitamin D Levels Indicative of Vitamin D Sufficiency: Implications for Establishing a New Effective Dietary Intake Recommendation for Vitamin D”.

The report concluded that “several studies have more accurately defined vitamin D deficiency as circulating levels of 25(OH)D less or even 80 nmol or 32 µg/L” and that “current daily recommendations for adults are not sufficient to maintain circulating 25(OH)D levels at or above this level, especially in pregnancy and lactation”.
For the CPT code(s) in the attached files, the patient should have the corresponding diagnosis (ICD-10-CM) code(s).

**ICD-10 Diagnosis Codes (Proven)**

CMP-038 Vitamin D
ICD10 v1.0
REFERENCES


POLICY HISTORY/REVISION HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
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<tbody>
<tr>
<td>01/21/2017</td>
<td>Updated ICD10 codes as per CMS recommendations. Removed ICD9 code file.</td>
</tr>
<tr>
<td>10/01/2015</td>
<td>Removed ICD9 table. Embedded ICD9/ICD10 PDF files.</td>
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